



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2023-N-4742]

Phibro Animal Health Corp.; Proposal to Withdraw Approval of New Animal Drug Applications for Carbadox in Medicated Swine Feed; Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or the Agency), Center for Veterinary Medicine (CVM), is proposing to withdraw approval of all new animal drug applications (NADAs) providing for use of carbadox in medicated swine feed, for which Phibro Animal Health Corp., Glenpointe Centre East, Third Floor, 300 Frank W. Burr Blvd., Suite 21, Teaneck, NJ 07666-6712, is the sponsor, and is announcing an opportunity for the holder of the NADAs to request a hearing on this proposal. This action is based on CVM's determination that there is no approved regulatory method to detect the residue of carcinogenic concern in the edible tissues of the treated swine.

DATES: The sponsor of the NADAs may submit a written request for a hearing by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Submit all data, information, and analyses upon which a request for a hearing relies by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Either electronic or written comments on the notice must be submitted by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: The request for a hearing may be submitted by the sponsor of the NADAs by either of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments to submit your request for hearing. Your request for a hearing submitted electronically, including any attachments to the request for hearing, to <https://www.regulations.gov> will be posted to the docket unchanged.

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper request for a hearing): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- Because your request for a hearing will be made public, you are solely responsible for ensuring that your request does not include any confidential information that you or a third party may not wish to be publicly posted, such as confidential business information (e.g., a manufacturing process). The request for a hearing must include the Docket No. FDA-2023-N-4742 for “Phibro Animal Health Corp.; Proposal to Withdraw Approval of New Animal Drug Applications for Carbadox in Medicated Swine Feed; Opportunity for a Hearing.” The request for a hearing will be placed in the docket and publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

The sponsor of the NADAs may submit all data and analyses upon which the request for a hearing relies in the same manner as the request for a hearing except as follows:

- Confidential Submissions--To submit any data and analyses with confidential information that you do not wish to be made publicly available, submit your data and analyses only as a written/paper submission. You should submit two copies total of all data and analyses. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the

claimed confidential information, in its consideration of any decisions on this matter.

The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov> or available at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday. Submit both copies to the Dockets Management Staff. Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law.

Comments Submitted by Other Interested Parties: For all comments submitted by other interested parties, submit comments as follows. Please note that late, untimely filed comments will not be considered. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else’s Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see “Written/Paper Submissions” and “Instructions”).

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2023-N-4742 for “Phibro Animal Health Corp.; Proposal to Withdraw Approval of New Animal Drug Applications for Carbadox in Medicated Swine Feed; Opportunity for a Hearing.” Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit

both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:

<https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Diane Heinz, Center for Veterinary Medicine (HFV-6), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 240-402-5692.

SUPPLEMENTARY INFORMATION:

I. Approved NADAs for Use of Carbadox in Swine Feed

Carbadox, a quinoxaline derivative, is a synthetic organic acid antimicrobial. Currently, there are three approved NADAs for use of carbadox in medicated swine feed, either by itself or in combination with other approved new animal drugs. Phibro Animal Health Corp., Glenpointe Centre East, Third Floor, 300 Frank W. Burr Blvd., Suite 21, Teaneck, NJ 07666-6712, is currently the sponsor of all three approved NADAs.

Carbadox is marketed as a Type A medicated article used to manufacture complete Type C medicated feeds that are administered ad libitum (available at all times) to swine. Carbadox is indicated for the control of dysentery and bacterial enteritis, and for growth

promotion. A tolerance of 30 parts per billion (ppb) has been established for residues of quinoxaline-2-carboxylic acid (QCA), the marker residue, in liver of swine (21 CFR 556.100). The combination products containing carbadox (carbadox and pyrantel, and carbadox and oxytetracycline) are also approved for additional indications related to the non-carbadox active ingredient.

The following three NADAs are approved for the use of carbadox:

NADA 041-061, originally approved in 1972 (37 FR 20683, October 3, 1972), provides for the use of MECADOX 10 (carbadox) Type A medicated article to manufacture single-ingredient Type C medicated swine feeds for the following conditions of use:

Carbadox at 10 to 25 grams per ton (g/ton) of feed for increased rate of weight gain and improved feed efficiency; and

Carbadox at 50 g/ton of feed for control of swine dysentery (vibrionic dysentery, bloody scours, or hemorrhagic dysentery); for control of bacterial swine enteritis (salmonellosis or necrotic enteritis caused by *Salmonella choleraesuis*); and for increased rate of weight gain and improved feed efficiency.

In January 1998, CVM approved a supplemental application to NADA 041-061, which included the approved method.

In October 1998, CVM approved an additional supplemental NADA for NADA 041-061, changing the withdrawal period for carbadox medicated feeds from 70 days to 42 days.

Currently, the withdrawal period for these uses of carbadox is 42 days (§ 558.115(d)(1)(ii) and (d)(2)(ii) (21 CFR 558.115(d)(1)(ii) and (d)(2)(ii))).

NADA 092-955, originally approved in 1975 (40 FR 45164, October 1, 1975), provides for the use of MECADOX 10 (carbadox) Type A medicated article with BANMINTH (pyrantel tartrate) Type A medicated article to manufacture two-way, combination drug Type C medicated swine feeds for the following conditions of use:

Carbadox at 50 g/ton of feed plus pyrantel tartrate at 96 g/ton of feed for control of swine dysentery (vibrionic dysentery, bloody scours, or hemorrhagic dysentery); for control of bacterial swine enteritis (salmonellosis or necrotic enteritis caused by *Salmonella choleraesuis*); as an aid in the prevention of migration and establishment of large roundworm (*Ascaris suum*) infections; and as an aid in the prevention of establishment of nodular worm (*Oesophagostomum*) infections.

The withdrawal period for the use of this drug combination is 70 days (§ 558.115(d)(3)(ii)).

NADA 141-211, originally approved in 2004 (69 FR 51173, August 18, 2004), provides for the use of MECADOX 10 (carbadox) Type A medicated article with TERRAMYCIN 50, TERRAMYCIN 100, or TERRAMYCIN 200 (oxytetracycline) Type A medicated articles to manufacture two-way, combination drug Type C medicated swine feeds for the following conditions of use:

Carbadox at 10 to 25 g/ton of feed plus oxytetracycline at levels in feed to deliver 10 mg oxytetracycline per pound of body weight for treatment of bacterial enteritis caused by *Escherichia coli* and *S. choleraesuis* susceptible to oxytetracycline; for treatment of bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline; and for increased rate of weight gain and improved feed efficiency.

The withdrawal period for the use of this animal drug combination is 42 days (§ 558.115(d)(4); § 558.450(e)(3)(iii)).

II. Basis for Withdrawal of Approval

FDA is providing notice of an opportunity for a hearing (NOOH) on CVM's proposal to withdraw approval of the NADAs providing for use of carbadox in medicated swine feeds. New evidence demonstrates that the Delaney Clause in section 512(d)(1)(I) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360b(d)(1)(I)), which requires that no residue of a

carcinogenic drug can be found in any edible portion of the animal after slaughter, applies because the Diethylstilbestrol (DES) Proviso exception is no longer met (see section III).

Section 512(e)(1)(B) of the FD&C Act provides grounds for withdrawal of approval of an NADA if new evidence not contained in such application or not available until after such application was approved, tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available when the application was approved, shows that the Delaney Clause, section 512(d)(1)(I) of the FD&C Act, applies to the drug. Under the Delaney Clause, the Secretary shall not approve a new animal drug application if “such drug induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal” (section 512 (d)(1)(I) of the FD&C Act). An exception to this general rule, referred to as the “DES Proviso,” allows for the approval of a carcinogenic new animal drug where FDA finds that, under the approved conditions of use: (1) The drug will not adversely affect the animals treated with the drug, and (2) no residues of the drug will be found by an approved regulatory method in any edible tissues of or in any foods yielded by the animal (section 512(d)(1)(I)(i) through (ii) of the FD&C Act).

Evidence available at the time of the approvals showed that carbadox was carcinogenic. At the time of the January 1998 supplemental approval, CVM concluded that carcinogenic residues, including desoxycarbadox (DCBX), a known carcinogenic metabolite of carbadox, depleted quickly (within 72 hours) while QCA residues depleted more slowly (Ref. 1). However, new evidence not available at the time of the approval, including studies conducted by the sponsor and submitted to FDA from 2005 to 2016 and a study conducted by a third party and summarized in a publication in 2022,¹ demonstrates that the residue of carcinogenic concern persists longer than previously known (Refs. 2 to 4). Because there is no established relationship

¹ “Metabolism and Tissue Depletion of Carbadox in Swine, Broilers, and Rats,” Jie Zhang, Wei Qu, Zongchao Wang, and Yuanhu Pan, *ACS Agricultural Science & Technology* 2022 2 (3), 477-485.

between concentrations of QCA measured by the approved method and concentrations of the residue of carcinogenic concern, the approved regulatory method cannot be used to measure the residue of carcinogenic concern.

Elsewhere in today's *Federal Register*, FDA is publishing a final order (Ref. 5) revoking the approved regulatory method for carbadox that measures QCA as a marker residue to detect the presence of any residue of carcinogenic concern (Ref. 6). Currently, therefore, there is no approved regulatory method for carbadox, and the second prong of the DES Proviso is not met.

III. Background Information Regarding the Regulation of Carcinogenic New Animal Drugs

Under the Delaney Clause of the FD&C Act, the Secretary shall not approve a carcinogenic new animal drug application unless the DES Proviso applies (section 512(d)(1)(I)(i) through (ii) of the FD&C Act). FDA has issued implementing regulations that set the requirements for demonstrating that no residues of the drug will be found by an approved regulatory method in any edible tissues of or in any foods yielded from the animal (21 CFR part 500, subpart E). These regulations, referred to as the sensitivity of the method regulations (SOM regulations), describe how FDA determines whether the regulatory method proposed by a sponsor is sufficiently sensitive to ensure that residues of carcinogenic concern in edible tissues will not exceed concentrations that represent no significant increase in the risk of cancer to humans.

Pursuant to these regulations, FDA determines for each drug and each drug metabolite (on the basis of the results of chronic bioassays and other information) whether the drug or any of its metabolites are carcinogenic (§ 500.84(a) (21 CFR 500.84(a))). For the drug and each metabolite determined to be carcinogenic, FDA calculates, based upon submitted assays, the concentration of the test compound in the total diet of the test animal that corresponds to a maximum lifetime risk of cancer in the test animal of 1 in 1 million (§§ 500.82(b) (21 CFR 500.82(b)) and 500.84(c)(1)). FDA designates the lowest value thus calculated as the S_o (§§ 500.82(b) and 500.84(c)(1)). The S_o corresponds to a concentration of residue of

carcinogenic concern in the total human diet that represents no significant increase in the risk of cancer to people (§ 500.82(b)). Residue of carcinogenic concern includes all compounds in the total residue of a demonstrated carcinogen excluding any compound judged by FDA not to present a carcinogenic risk (§ 500.82(b)). The total residues of carcinogenic concern (the drug and all of its metabolites less metabolites shown to be noncarcinogenic) are regulated based on the most potent carcinogenic residue (§ 500.84(c)(1)). This approach ensures that use of the drug does not present a significant increase in the risk of cancer when considering all residues in edible tissues.

Because the total diet is not derived only from food-producing animals, the SOM regulations make adjustments for human food intake of edible tissues and determine the concentration of residues of carcinogenic concern in a specific edible tissue that corresponds to no significant increase in the risk of cancer to the human consumer. FDA assumes for purposes of these regulations that this value will correspond to the concentration of residues in a specific edible tissue that corresponds to a maximum lifetime risk of cancer in test animals of 1 in 1 million. This value is termed the S_m (§§ 500.82(b) and 500.84(c)(1)).

Based on residue depletion data submitted by a sponsor, FDA selects a target tissue (the edible tissue selected to monitor for residues in the target animals) and a marker residue (a residue whose concentration is in a known relationship to the concentration of the residues of carcinogenic concern in the last tissue to deplete to the S_m) and designates the concentration of the marker residue that the regulatory method must be capable of detecting in the target tissue (§ 500.86(a) through (c) (21 CFR 500.86(a) through (c))). This value, termed the R_m , is the concentration of a marker residue in the target tissue when the residue of carcinogenic concern is equal to S_m (§ 500.82(b)). When the marker residue is at or below the R_m , the residue of carcinogenic concern in the human diet does not exceed S_o (§ 500.86(c)). This regulation ensures that when the marker residue is no longer detectable, the residue of carcinogenic concern does not exceed S_m in any of the edible tissues (§§ 500.82(b) and 500.86(c)).

A sponsor must submit a regulatory method that is able to detect the marker residue at or below the R_m (21 CFR 500.88(b) and 500.84(c)(2)) (“The LOD [Limit of Detection for the regulatory method] must be less than or equal to R_m .”). If a method is not developed that can detect the marker residue at or below the R_m , the requirements of the SOM regulations are not satisfied, and FDA cannot approve the drug. The DES Proviso and FDA’s implementing regulations are satisfied where no marker residue is detectable using the approved regulatory method under the proposed conditions of use of the drug, including the proposed preslaughter withdrawal period (§ 500.84(c)(3)).

IV. Notice of Opportunity for a Hearing

CVM is proposing to withdraw approval of the three NADAs that provide for use of carbadox in swine feed because new evidence demonstrates that the drug does not meet the DES Proviso exception to the Delaney Clause. There is currently no approved regulatory method for carbadox.

Therefore, notice is given to Phibro Animal Health Corp., Glenpointe Centre East, Third Floor, 300 Frank W. Burr Blvd., Suite 21, Teaneck, NJ 07666-6712, and to all other interested persons, that the Deputy Commissioner for Policy, Legislation, and International Affairs, Office of Policy, Legislation, and International Affairs proposes to issue an order under section 512(e) of the FD&C Act withdrawing approval of all NADAs providing for use of carbadox in medicated swine feed.

In accordance with section 512 of the FD&C Act and 21 CFR part 514 and under the authority delegated to the Deputy Commissioner for Policy, Legislation, and International Affairs, Office of Policy, Legislation, and International Affairs by the Commissioner of Food and Drugs, Phibro Animal Health Corp., the sponsor, is hereby given an opportunity for a hearing to show why approvals of NADA 041-061, 092-955, and 141-211 should not be withdrawn.

If the sponsor, Phibro Animal Health Corp., wishes to request a hearing, the sponsor must file the following: (1) a written notice of participation and request for a hearing (see DATES and ADDRESSES) and (2) the data, information, and analyses relied on to demonstrate that there is a genuine and substantial issue of fact that requires a hearing (see DATES and ADDRESSES).

Any other interested person may also submit comments on this notice. Procedures and requirements governing this NOOH, a notice of appearance and request for a hearing, submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of a hearing, are contained in § 514.200 (21 CFR 514.200) and 21 CFR part 12.

The failure of a holder of an approval to timely file a request for a hearing as required by § 514.200 constitutes an election by the holder not to avail itself of the opportunity for a hearing and constitutes a waiver of any contentions concerning the legal status of any such drug product, and the Director of CVM will summarily enter a final order withdrawing the approvals. Any new animal drug product marketed without an approved NADA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that there is no genuine and substantial issue of fact that precludes the withdrawal of approval of the applications, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person who requests a hearing, making findings and conclusions, and denying a hearing.

If a hearing is requested and is justified by the sponsor's response to this NOOH, the issues will be defined, a presiding officer will be assigned, and a written notice of the time and place at which the hearing will commence will be issued as soon as practicable.

This notice is issued under section 512 of the FD&C Act and under the authority delegated to the Deputy Commissioner for Policy, Legislation, and International Affairs, Office of Policy, Legislation, and International Affairs.

V. Environmental Impact

The Agency has determined under 21 CFR 25.33(g) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. References

The following references are on display in the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <https://www.regulations.gov>. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

1. FDA, Freedom of Information Summary, NADA 041-061, MECADOX 10 (carbadox) Type A medicated article, supplemental approval January 30, 1998. Available at <https://animaldrugatfda.fda.gov/adafda/app/search/public/document/downloadFoi/308>.

2. Evaluations of the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA). Carbadox. 2021. Available at: <https://apps.who.int/food-additives-contaminants-jecfa-database/Home/Chemical/2176>.

3. Memorandum to File entitled “CVM Response to Phibro Animal Health Corporation’s September 18, 2020 Comments on CVM’s July 20, 2020 Proposed Order to Revoke the Regulatory Method for Carbadox” (January 6, 2022).

4. Memorandum to File entitled “CVM review of comments on the Zhang article that Phibro references in the document submitted to the Part 15 Hearing docket under cover letter

dated June 9, 2022, and entitled, ‘Phibro Animal Health Corporation’s Reply to the January 6, 2022 ‘CVM Response to Phibro Animal Health Corporation’s September 18, 2020 Comments on CVM’s July 20, 2020 Proposed Order to Revoke the Regulatory Method for Carbadox.’” (October 30, 2023).

5. Phibro Animal Health Corp.; Carbadox in Medicated Swine Feed; Revocation of Approved Method ([INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]).

6. “Determination of Carbadox as Quinoxaline-2-carboxylic Residues in Swine Liver and Muscle Tissues after Drug Withdrawal.” Available at <https://www.fda.gov/media/136267/download>.

Dated: November 1, 2023.

Kimberlee Trzeciak,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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